The European Association of Medical devices Notified Bodies

Team-NB Position Paper

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Demonstration of Safety and Performance for Combinatorial Use of Reagent Devices with other devices or Equipment

Introduction & Scope

This document aims to provide harmonized Notified Bodies expectations concerning the demonstration of safety and performance for reagent devices intended to be used in combination with other devices or equipment/instruments. It aims to clarify key considerations for ensuring compliance with the relevant regulatory framework under Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) and shall be understood as a supporting guidance to the "Team-NB Position Paper: Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746".

The document provides guidance on how manufacturers should adequately demonstrate the compatibility, safety, and performance of combined devices, including the connection system where applicable. Furthermore, it explores the essential role of risk assessment, performance evaluation and information provided to the user for devices that are intended to be used in combination with other devices or equipment. Following potential combinations will be discussed below:

- closed system or defined combination
    - e.g., reagent is only compatible with one specific instrument
    - e.g., reagent can be used on different, but specified, instruments and/or accessories
- open system
    - e.g., reagent can be use on similar general lab equipment/instruments

Specific requirements of Regulation (EU) 2017/746

For devices intended for use in combination with other devices or equipment, Regulation (EU) 2017/746 defines specific requirements for the general safety and performance (Annex I) and the content of the technical documentation (Annex II):

1. **Annex I, Chapter II, Section 13.1**:

    - If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system, shall be safe and shall not impair the specified performances of the devices.

- Any restrictions on use applying to such combinations shall be indicated on the label and/or in the instruction for use (IFU).

2. **Annex I, Chapter III, Section 20.4.1 (j)**:

   For devices intended for use in combination with or installed with or connected to other devices and/or general purpose equipment:

   - information to identify such devices or equipment, in order to obtain a validated and safe combination, including key performance characteristics, and/or
   - information on any known restrictions to combinations of devices and equipment.

3. **Annex II, Section 1.1 (m)**:

   A description of the accessories for a device, other devices and other products that are not devices, which are intended to be used in combination with the device.

4. **Annex II, Section 6.5 (d):**

   If the device is to be connected to other equipment in order to operate as intended, a description of the resulting combination including proof that it conforms to the general safety and performance requirements set out in Annex I when connected to any such equipment having regard to the characteristics specified by the manufacturer.

Note:
Article 1 (3a) of the IVDR which states that Regulation (EU) 2017/746 does not apply to products intended for general laboratory use or research-use only (RUO), unless, based on their characteristics, such products are specifically intended by their manufacturer to be used for in vitro diagnostic examinations.
Products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination fall under IVDR **Annex VIII Rule 5** class A.

General Considerations and Expectations of Notified Bodies

To align with the expectations of notified bodies in demonstrating safety and performance for combinatorial use, the manufacturer must provide a Technical Documentation that fulfils all applicable requirements of Regulation (EU) 2017/746 Annex I-III. In particular, the manufacturer must

1. Ensure a Safe Combination: Considerations for risk assessment and performance evaluation of devices intended to be used in combination

Annex I, Chapter II, Section 13.1 specifies that combinatorial systems must be safe and shall not impair the specified performances of the devices. As the IVDR does not define explicit rules to obtain evidence supporting these claims manufacturers bear the responsibility of generating robust, reproducible data to address the notified bodies' expectations.

To ensure compliance with IVDR requirements, manufacturers must conduct thorough assessments of the following aspects for devices intended for combination use:

- **Risk Assessment**

  When a manufacturer claims that a device is suitable for (unrestricted) combinatorial use, adequate evidence must be presented. The manufacturer shall:

  - Identify risks associated with the combinatorial use of the device with other devices and/or electrical equipment/instruments (this includes, but might be not limited to, operating conditions, calibration, maintenance, and disposal).
  - Apply appropriate risk mitigations (e.g., safety by design, information for safety) to reduce the likelihood of unsafe or ineffective combinations
  - demonstrate that the combination of devices does not introduce new hazards or compromise safety, including risk assessments aligned with ISO 14971.

- **Performance Evaluation**

  - Provide traceable and reproducible results demonstrating that the combined system performs as intended. Where applicable, key performance characteristics according to IVDR Annex I, 9a and b must meet predefined acceptance criteria.

Failure to appropriately address these points could result in requests for additional data or rejections by the notified bodies.

For **"closed systems"** where a device can be used in only one combination or in several, but defined combinations, a full performance evaluation is required (for at least one combination if more are claimed)**.** For any further combinations, equivalence in performance across the entire measurement range shall be demonstrated and a rationale provided to justify this approach.

Additionally, a declaration by the manufacturer specifying which other critical parameters based on Regulation (EU) 2017/746 Annex I, 9a and b must be considered for the other combinations is required. In addition, a rationale shall be presented in the Technical Documentation why certain parameters do not need to be tested and/or why certain data (e.g., clinical data in particular) are transferable.

If equivalent performance cannot be demonstrated, a full performance evaluation is expected for each combination.

Examples where performance studies are expected with the specific device combinations include, but are not limited to:

- PCR kit which is combined with an extraction instrument. Extraction instrument if the extraction efficiency and yield could influence the test result (e.g. virus/bacteria detection)
- PCR- kit which is combined with a real-time PCR cycler including software version
- Coagulation device that can be used on multiple instruments. Different coagulation analyzers
- Device measuring total cholesterol using different instruments Different clinical chemistry instruments
- SaMD (under the Software Life Cycle — software-to-software interoperability and compatibility with different Laboratory Information Systems [LIS])

For **"open systems"** where a device can be used in combination with more simple general lab equipment/instruments from any brand, the manufacturer shall define (with appropriate justification) the critical characteristics and specifications that this lab equipment/instruments must possess. A full performance evaluation is required for the device under review with a general lab equipment/instrument from any brand that fulfills the specified critical characteristics and specifications.

Examples for which the indication of specifications might be sufficient (with appropriate justification) include, but are not limited to:

- ELISA plate reader (e.g., wavelength)
- Liquid Handling instruments (e.g. precision)
- Endpoint PCR cycler
- Extraction kit, extraction instrument when requirement on purity and concentration is defined in the IFU (e.g., in combination with PCR devices for gene expression analysis, detection of mutations or deletions, sequence analyses (WES, WGS), etc.)

Special case: Products or equipment listed as general laboratory use or Research-Use Only (RUO) Products*

* "research-use only" as mentioned in preamble 7 and Article 1, Section 3 (a) of the IVDR.

Article 1 of the IVDR defines that products or equipment listed as general laboratory use or research use only products are not covered by the IVDR unless they are intended for in vitro diagnostic purposes. In such cases, CE-marked devices/equipment should be used, if available, in combination with the device. When an IVD manufacturer intends to include specific general laboratory use or RUO

products/equipment in combination claims, manufacturers must substantiate their combination claims with sufficient evidence to demonstrate alignment with IVDR requirements for safety and performance. The notified bodies will require detailed rationale and supporting documentation under these circumstances. In such cases it should be clear to the IVD manufacturer that they have the full responsibility for the safety and performance in the combinatorial workflow.

Please also refer to MDCG 2024-11 for guidance on qualification of in vitro diagnostic medical devices, specifically section 2.4.

Examples of products for general laboratory use might include, but are not limited to:

- PCR cycler
- Nucleic acid extraction kits
- ELISA plate reader
- Next Generation Sequencing platform
- HPLC products
- Mass spectrometer

2. Emphasize Labeling Clarity: Information provided to the user

Regulation (EU) 2017/746 Annex I, 20.4.1 (j) defines information to be provided to the user for devices intended for use in combination with or installed with or connected to other devices and/or general purpose equipment. It is the Notified Bodies expectation that the following information is provided to the user:

- Information to identify devices, accessories, equipment, or instruments (including their key performance characteristics, if applicable) intended to be used in combination with the device. For devices that can be used in combination with general lab equipment/instruments from any brand, the critical characteristics that this lab equipment/instruments must possess shall be defined.

- Information on any known restrictions (e.g., incompatibility or interference).

- sufficient functional details to ensure correct user integration of the combined system, including methodologies for connection or data exchange.

- unambiguous warnings or limitations where compatibility may impact safety or impair performance.

The provided information must be easy to interpret and act upon for the intended user.

3. Post-market surveillance (PMS) requirements

Follow the general obligations as referred to in Regulation (EU) 2017/746, Article 78 and Annex III, with the specific focus on the safety and performance for the claimed combinatorial use workflows.

The performance of the claimed combinations shall be continuously monitored in order to ensure their safety and performance. Feedback and complaints from users regarding their experience with the combined use of the devices shall be taken into account to make corrections to the labelling if required or to identify new risks.

Conclusion

Under Regulation (EU) 2017/746, manufacturers must ensure the safety and performance of devices used in combination with other devices or instruments. While the regulation does not define explicit rules for validating combinatorial claims, notified bodies expect clear, robust, and reproducible evidence supporting these claims. Manufacturers must prioritize comprehensive validation, risk mitigation, and transparency in labelling and IFU to align with these expectations.

This position paper is a supporting guidance to the “Team-NB Position Paper: Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746”. It reflects the shared understanding and expectations of notified bodies related to the combinatorial use of reagent devices with other devices or equipment and aims to provide a reference for consistent application of IVDR provisions.